Journal of Pediatric Surgery 56 (2021) 580–586

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Retrospective analysis of outcomes in patients with clear cell sarcoma of the kidney: A tertiary single-institution experience☆,☆☆,★,★★

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ARTICLE INFO

Article history:
Received 2 April 2020
Received in revised form 15 July 2020
Accepted 17 July 2020

Key words:
Clear cell sarcoma
Pediatric renal tumor
Wilms' tumor
Treatment

ABSTRACT

Background: Clear cell sarcoma of the kidney (CCSK) is a rare and aggressive tumor. This study aims to describe the clinical characteristics and outcomes of CCSK patients in one of the largest pediatric medical centers in China.
Methods: We included all patients diagnosed with CCSK between January 2008 and March 2019 at the Children's Hospital of Chongqing Medical University, China. The patients' demographics, clinical presentation, and management were reviewed. Follow-up was continued until December 2019.
Results: In total, 41 CCSK patients (66% male) with a median age of 24 months (range 3-108 months) were identified. The stage distributions of stages I, II, III and IV were 42%, 34%, 24% and 0%, respectively. Preoperative chemotherapy was administered to 7/41 patients. All patients underwent radical nephrectomy and postoperative chemotherapy. The median number of lymph nodes sampled was 4 (range 1–12). Radiotherapy was applied in 8/41 patients. The 5-year event-free survival (EFS) and overall survival (OS) were 63.9% and 78.8%, respectively. Of the 41 patients, 11 patients experienced relapse at a median time of 19 months (range 5-72 months). The most common site of recurrence was the tumor bed (9/11). Young age was a significant adverse prognostic factor for EFS.
Conclusions: The overall outcome of CCSK patients in our hospital is poorer than that in developed regions. More research is needed to clarify the underlying causes of poorer outcomes in young patients and improve outcomes.
Type of study: Retrospective study.
Level of evidence: LEVEL IV.

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Clear cell sarcoma of the kidney (CCSK) is an uncommon renal tumor that comprises approximately 5% of all primary renal tumors in children and is the second most common pediatric renal tumor following Wilms' tumor (WT) [1,2]. Historically, CCSK has inferior survival compared to WT due to its high metastatic potential as an aggressive tumor [3,4]. The overall survival (OS) has been improved from 25% to 90% for patients undergoing intensive chemotherapy and radiotherapy [5,6], and a similar outcome was reported in the International Society of Pediatric Oncology (SIOP) trial [7]. Because CCSK is a rare entity, limited research on the characteristics and outcomes of CCSK patients has been reported in other regions of the world, especially in developing countries [8,9]. In this study, we reviewed our experience to reveal the clinical characteristics and outcomes of CCSK in a developing country.

1. Patients and methods

1.1. Patients

All patients presenting between 2008 and 2019 with a final diagnosis of CCSK were reviewed and followed up until December 2019. The collected data included demographics, clinical presentation, radiological,

Abbreviations: CCSK, Clear cell sarcoma of the kidney; WT, Wilms' tumor; NWTS, National Wilms Tumor Study Group; SIOP, International Society of Pediatric Oncology; OS, Overall survival; EFS, Event-free survival; LNS, Lymph nodes.

☆ Funding: There was no funding for this manuscript.

☆☆ Conflict of Interest: The authors declare that they have no conflict of interest.

★ Research involving human participants: This study was approved by the ethics committee of Children's Hospital of Chongqing Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

★★ Informed Consent: Written informed consent was obtained from individual participants.

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https://doi.org/10.1016/j.jpedsurg.2020.07.022
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surgical, and medical management, and clinical outcome. All patients involved in the study were classified according to the National Wilms Tumor Study Group (NWTS) surgical pathology staging system [10,11].

1.2. Treatment

Chest computed tomography (CT) scan and abdominal contrast-enhanced CT scan were performed for all patients before the treatment plan. Whether to perform radical nephrectomy or preoperative chemotherapy was first discussed by the urologist specialists according to the abdominal contrast-enhanced CT, and a consensus was reached. Lymph node sampling was performed in all children during surgery. However, if the great vessels, such as aorta ventralis and postcava, were invaded, which may obviously increase the perioperative risks, the final decision was made by a departmental discussion. We first recommend preoperative chemotherapy.

Preoperative chemotherapy included weekly vincristine (VCR) (1.5 mg/m2) and twice-weekly dactinomycin (ACTD) (0.045 mg/kg) for a period of 4–6 weeks, which originated from the SIOP protocol [7]. Postoperative chemotherapy included VCR, doxorubicin, and cyclophosphamide, alternating with cyclophosphamide and etoposide for 24 weeks, and postoperative radiotherapy (10.8 Gy), which originated from the NWTS-5 protocol [6].

Radiotherapy treatment was advised for all children after radical nephrectomy, but it was not administered to all children because of socioeconomic issues. Because there is no radiotherapy equipment in our children's hospital, we had to recommend the patients who needed radiotherapy to the general hospital.

1.3. Imaging

Tumor volume was calculated using the ellipsoid formula (length [cm] * width [cm] * depth [cm] * 0.523 cm^3 = volume [ml]). Response Evaluation Criteria in Solid Tumors (RECIST) categories were calculated using the largest dimension: complete response (CR) = 100% decrease in the largest tumor dimension after preoperative chemotherapy; partial response (PR) = 30% decrease in the largest tumor dimension; minor response (MR) = 12% but <30% decrease in the largest tumor dimension; stable disease (SD) = increase in the largest tumor dimension <20% and decrease in the largest tumor dimension <12%; and progressive disease (PD) = increase in the largest tumor dimension ≥20% [12].

1.4. Statistical analysis

Statistical analysis was performed using SPSS version 21.0. Qualitative or categorical variables are expressed as frequencies and proportions. The data are expressed as the median [range]. Survival functions for event-free survival (EFS) and OS were obtained by the Kaplan-Meier method. Log-rank tests and Cox regression models were used to compare survival among different subgroups. EFS was defined as the time from the start of treatment to disease progression, recurrence, or death as the first event. OS was defined as the time from the start of treatment to death regardless of the cause. Patients were censored at the time of the last follow-up record.

2. Results

2.1. Patient characteristics

Among 271 patients diagnosed at our hospital with renal tumors, 41 patients were diagnosed pathologically as CCSK, constituting 15.1% of renal tumors. The patient characteristics are listed in Table 1. The median age of the children at diagnosis was 24 months (range 3–108 months). The male:female ratio of these patients was 1.93 (27:14), and an imbalanced distribution also occurred between left- and right-sided tumors, with a ratio of 3.1 (31:10). Presenting symptoms included abdominal mass, 23 (58.9%); hypertension, 11 (28.2%); hematuria, 10 (25.6%); abdominal pain, 5 (12.8%); fever, 4 (10.26%); anemia, 2 (5.1%); headache and dizziness, 2 (5.1%); and vomiting, 1 (2.6%); accidental discovery occurred in 1 (2.6%). Four (10.26%) patients were associated with a congenital abnormality: 2 patients with umbilical hernia, 1 patient with right inguinal hernia, and 1 with right cryptorchidism. The stage distributions for stages I, II, and III were 42%, 34%, and 24%, respectively (Table 1). None of the patients had distant metastases (stage IV) or bilateral tumors (stage V). Tumor rupture in surgery occurred in 3/41 patients. Abdominal lymph node metastases were present at the time of nephrectomy in 5/41 cases. Additionally, inferior vena cava infiltration and diaphragm infiltration were detected during surgery in one patient each and managed successfully. The median number of lymph nodes (LNS) sampled was 4 (range 1–12). The resected lymph nodes were not quantified in 3 (7.3%) patients, 1–5 LNS were sampled in 30 patients (73.2%), 6–10 LNS were sampled in 6 patients (14.6%), and ≥11 LNS were sampled in 2 (4.9%) patients. The occurrence of LNS involvement was 1, 2, and 2 in the 1–5 group, 6–10 group and ≥11 group, respectively.

Table 1
Patient characteristics.

Item	n (%)
Sex	
Male	27 (66%)
Female	14 (34%)
Localization	
Left	31 (76%)
Right	10 (24%)
Age (months)	
Median (range)	24 (3-108)
Symptoms	
Abdominal mass	23 (58.9%)
Hypertension	11 (28.2%)
Fever	4 (10.3%)
Hematuria	10 (25.6%)
Abdominal pain	5 (12.8%)
Anemia	2 (5.1%)
Headache and dizziness	2 (5.1%)
Vomiting	1 (2.6%)
Incidental discovery	1 (2.6%)
Congenital abnormality	
Umbilical hernia	2 (5.1%)
Inguinal hernia	1 (2.6%)
Cryptorchidism	1 (2.6%)
Lymph nodes sampled	
Median (range)	4 (1-12)
Unknown	3 (7.3%)
1-5	30 (73.2%)
6-10	6 (14.6%)
≥11	2 (4.9%)
Overall stage distribution	
I	17 (42%)
II	14 (34%)
III	10 (24%)
IV	0 (0%)
Local stage III specified	
Positive lymph nodes	5 (12.2%)
Tumor rupture	3 (7.3%)
Inferior vena cava thrombosis	1 (2.6%)
Diaphragm infiltration	1 (2.6%)

2.2. Treatment

All patients had successful radical nephrectomy either upfront (34 patients) or after preoperative chemotherapy (7 patients). The stage distribution among the 7 patients included 5 stage III (2 lymph node-positive and 1 tumor rupture, inferior vena cava infiltration, and diaphragm infiltration each) and 2 stage II (both were renal venous thrombus and underwent radical resection). The mean tumor volume in surgery was 604 cm^3, ranging from 14 cm^3 to 1,842 cm^3. The mean tumor volume among the 7 patients who received preoperative chemotherapy was significantly greater than that among the other 34 patients who received

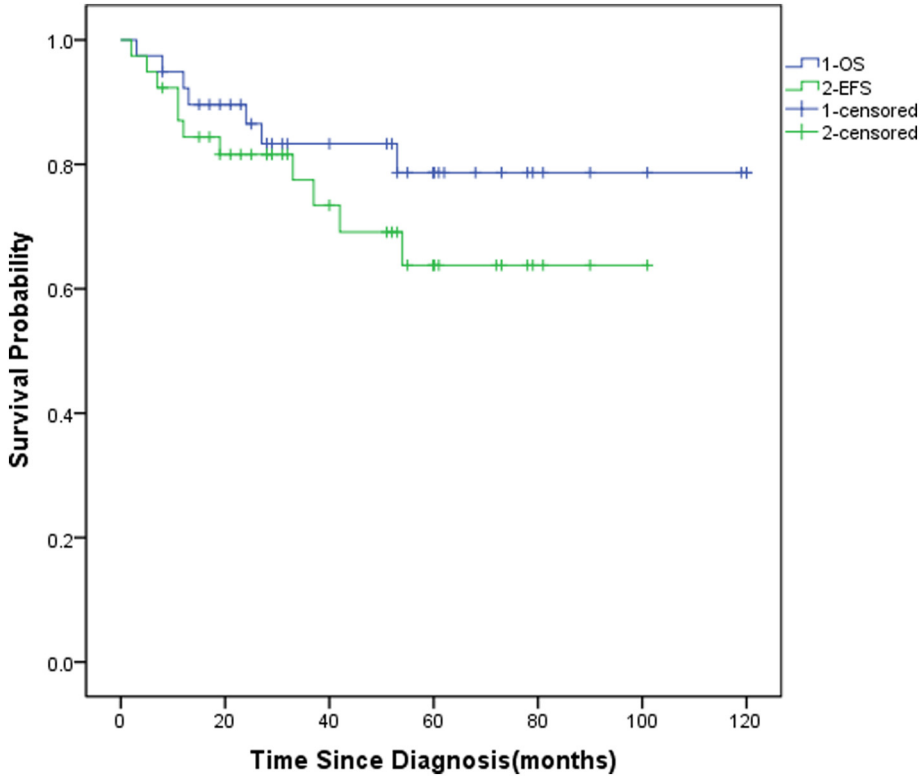

Fig. 1. OS and EFS for all patients.

upfront nephrectomy. (1,214 cm^3 vs 430 cm^3, $p<0.05$). In total, 7 patients did not experience a reduction in the tumor volume, only 1 patient obtained PR, 3 had SD, and the other 3 had PD. The mean tumor volumes before and after chemotherapy were 1,214 cm^3 and 1,270 cm^3, respectively. Only 8 patients received radiotherapy after radical nephrectomy, while the others did not receive radiotherapy.

2.3. Outcome

Follow-up continued until December 2019, with a median follow-up period of 40 months (range 8-120 months). Two patients were lost to follow-up in the 3rd month and 5th month. At the end of the follow-up period, the 5-year EFS rate was 63.9%, and the 5-year OS rate was 78.8% (Fig. 1).

Relapses occurred in 11 patients; the most common sites of relapses were the tumor bed only (n = 7), brain only (n = 1), tumor bed combined with the brain (n = 1), tumor bed combined with inferior vena cava tumor embolus (n = 1), and bone combined lungs (n = 1). The median time to relapse was 19 months (range 5-72 months), and the longest time for relapse was 72 months, which was a relapse in the tumor bed. In total, 7 patients died at the last follow-up time as follows: 6 patients died because of tumor relapse, and 1 patient died due to septic shock during chemotherapy. The treatment for relapsed CCSK varied and is summarized in Table 2.

Table 2
Patients with relapsed clear cell sarcoma of the kidney.

N	Age	Initial treatment regimen	Time to relapse [a]	Site of relapse	Surgery	Chemotherapy regimen	Outcome [b]
1	14	Regimen 1	72	Tumor bed	Yes(sCR)	OPAC/OPEC	NED 36 m
2	26	Regimen 1	42	Tumor bed	No	OPAC/OPEC	DOD 5 m
3	16	DD4A	12	Tumor bed	Yes(sCR)	OPAC/OPEC	DOD 23 m
4	7	Regimen 1	19	Tumor bed	Yes(sCR)	OPAC/OPEC	DOD 8 m
5	8	Regimen 1	5	Tumor bed	No	No	DOD 4 m
6	54	DD4A	37	Tumor bed	Yes(sCR)	RT + OPAC/OPEC	NED 25 m
7	7	Regimen 1	11	Brain	No	No	DOD 2 m
8	30	Regimen 1	33	Tumor bed + inferior vena cava embolus	Yes(nCR)	OPAC/OPEC	AWD[c] 40 m
9	18	Regimen 1	11	Tumor bed + brain	Yes(sCR)	OPAC/OPEC	Died of sepsis 4 m
10	53	Regimen 1	7	Bones + lungs	No	OPAC/OPEC	DOD 24 m
11	11	Regimen 1 + RT	54	Tumor bed	Yes(sCR)	OPAC/OPEC	NED 90 m

Abbreviations: RT, radiotherapy; AWD, alive with disease; DOD, dead of disease; NED, no evidence of disease; m, month(s); S, surgery; sCR, complete surgical remission; nCR, non-complete remission
Chemotherapy regimen:

OPAC: Vincristine 1.5 mg/m^2 (d1), Cyclophosphamide 1.2 g/m^2 (d1); Cisplatin 90 mg/m^2 (d2); Pharmorubicin 30 mg/m^2 (d4)
OPEC: Vincristine 1.5 mg/m^2 (d1), Cyclophosphamide 1.2 g/m^2 (d1); Carboplatin 400 mg/m^2 (d2); Etoposide 160 mg/m^2 (d4)
OPAC and OPEC were alternated each month; the course of treatment was 12-18 months

[a] Time after date of initial diagnosis.
[b] Time after last treatment for relapse.
[c] Alive with inferior vena cava embolus.

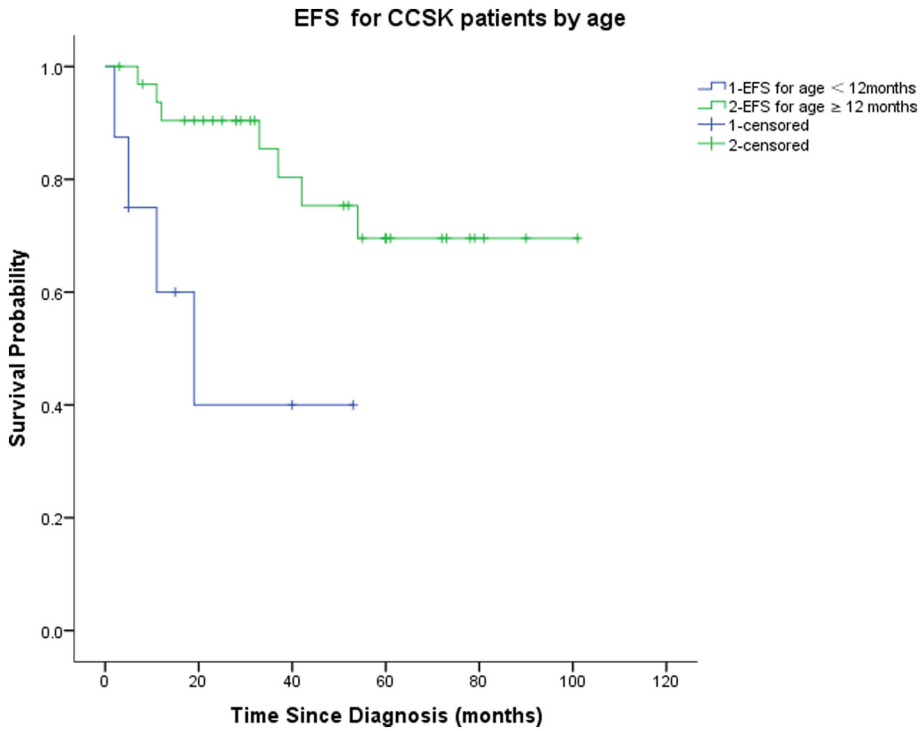

Fig. 2. EFS for CCSK patients by age.

Patients younger than 12 months (n = 8) who received chemotherapy in 50% reduction doses had a poorer 5-year EFS of 40% (p = 0.0003) and OS of 38.9% (p = 0.009) than the 5-year EFS of 69.5% and OS of 87.5% in patients older than 12 months (n = 33) (Figs. 2 and 3). Of the 8 patents who received radiotherapy, only 1 stage III patient experienced relapse in the tumor bed. There is no significant difference in the 5-year EFS of 87.5% and 5-year OS of 87.5% in the radiotherapy group compared with the 5-year EFS of 61.3% (p = 0.55) and 5-year OS of 77.8% (p = 0.85) in the non-radiotherapy group (n = 33) (Figs. 4 and 5); because the sample is limited, the radiotherapy group may have a superior outcome to the non-radiotherapy group. Cox regression analysis showed that age younger than 12 months was a significant adverse prognostic risk factor for EFS (p = 0.0183), while sex, tumor site, tumor volume, stage, preoperative chemotherapy, and radiotherapy were not associated with EFS in the current study (Table 3).

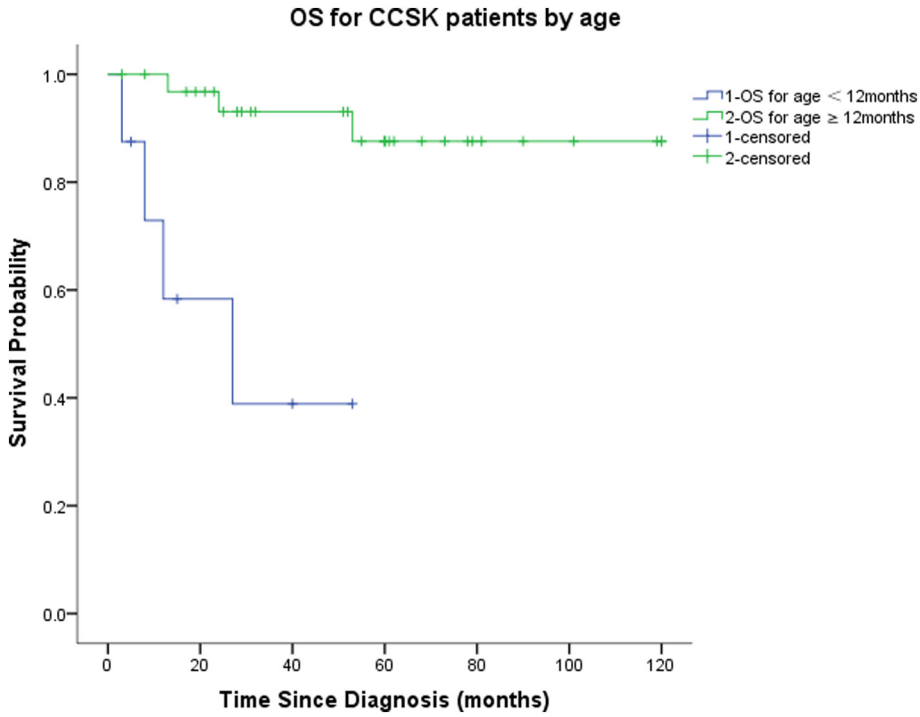

Fig. 3. OS for CCSK patients by age.

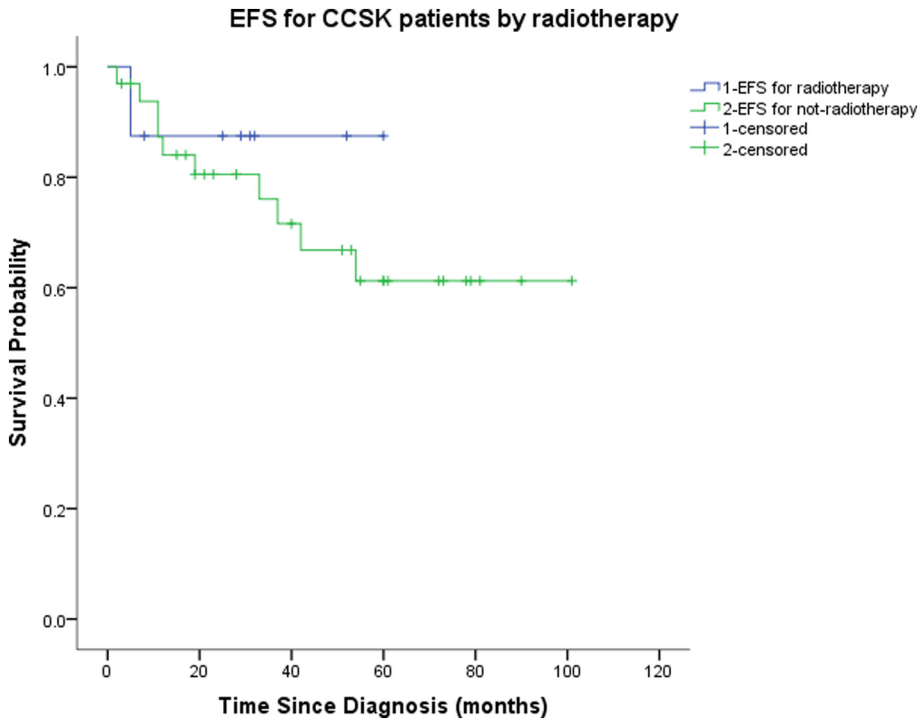

Fig. 4. EFS for CCSK patients by radiotherapy.

An 11-month-old boy and a 70-month-old girl received only postoperative chemotherapy for 2 weeks and 6 weeks, respectively. Because of economic issues, they discontinued chemotherapy treatment without any other procedures; fortunately, both of them recovered well without relapse. Two patients were misdiagnosed as favorable WT and received DD4A regimen chemotherapy, both of whom relapsed in the local region in the 12th month and 37th month.

3. Discussion

CCSK is a rare tumor in children and represented 15.1% of all renal tumors in our study, which is a significantly higher proportion than that in other studies. For example, the proportion ranged from 2.5% to 5% in European studies [2,7]. Similarly, a high proportion (11.2%) of CCSK in renal tumors was reported in the Japan Wilms Tumor Study-2

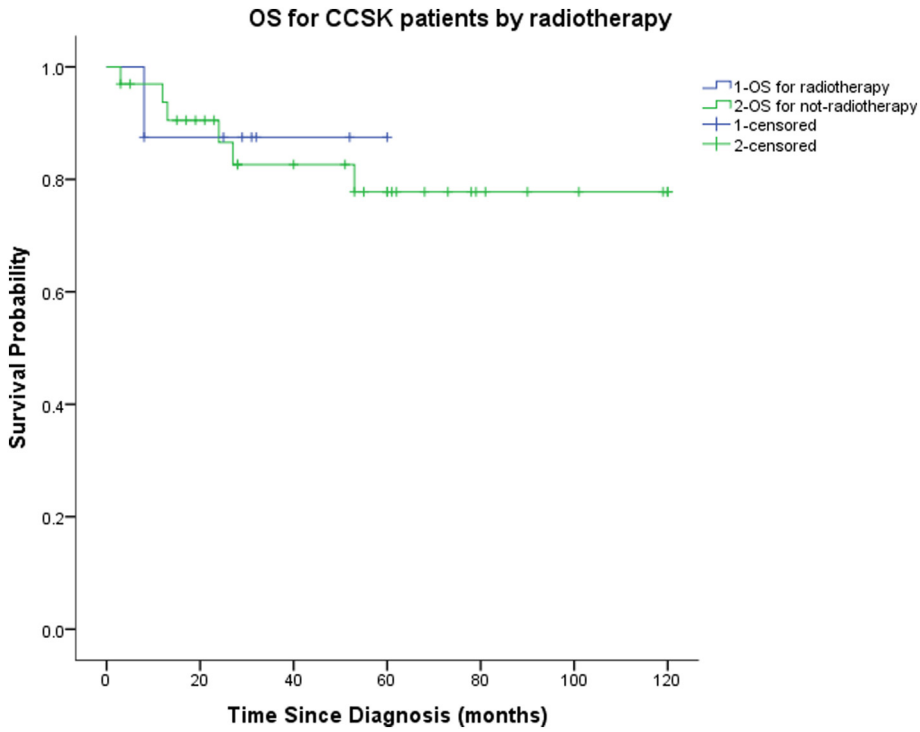

Fig. 5. OS for CCSK patients for radiotherapy.

Table 3
Univariable Cox regression of EFS.

Variable	N	p (per subgroup)	HR (lower 95%–upper 95%)	p (total group)
Sex				0.79
Female	14	1		
Male	27	0.7916	1.18 (0.345–4.035)	
Age group				0.02
Age≥12 m	33	1		
Age<12 m	8	0.0183	4.693 (1.299–16.95)	
Tumor site				0.96
Right	10	1		
Left	31	0.9606	0.967 (0.255–3.663)	
Stage				0.527
I	17	1		
II	14	0.6012	1.491 (0.333–6.673)	
III	10	0.2615	2.362 (0.527–10.592)	
Preoperative chemotherapy				0.87
Yes	7	1		
No	34	0.8668	1.122 (0.293–4.291)	
Tumor volume at surgery				0.39
Per unit	41	0.3863	0.999 (0.998–1.001)	
Radiotherapy				0.56
No	33	1		
Yes	8	0.5561	0.538 (0.068–4.241)	

(JWiTS-2) study [13]. Thus, more data is needed to determine whether the epidemiology of CCSK in Asia is different from other regions.

The median age of patients with CCSK at presentation ranges from 22 months to 46 months [6–9] and was 26.8 months in this study. Three (7.3%) patients were <6 months of age at the time of diagnosis; diagnosis within the first 6 months of age is rare, and most of these cases are case reports [14,15]; the youngest patient was a fetus (at 31 weeks gestation) [16]. Similar to other CCSK series [3,6–9], a male predominance (1.93:1) was noted in this study.

The accurate diagnosis of CCSK is difficult. In this study, 2 patients were misdiagnosed with favorable WT histology, resulting in mismatched neoadjuvant chemotherapy after radical nephrectomy. Unfortunately, the two patients relapsed during the follow-up time. The differential diagnosis of CCSK includes WT, mesoblastic nephroma, malignant rhabdoid tumor of the kidney, primitive neuroectodermal tumor, and renal cell carcinoma of the clear cell type [3]. Misdiagnosis leading to mismatched chemotherapy is not uncommon in CCSK [9], emphasizing the challenge for pathologists. In the SIOP [7] study, the initial diagnosis of different renal tumors was 27%, stressing the importance of a central review by expert pathologists or multicenter diagnoses.

As a common phenomenon, LNS are the most common metastatic sites in CCSK [2]. In addition, 5 (12.2%) patients exhibited LNS involvement at presentation, which is similar to another clinical trial (12%) [9]; however, LNS involvement was slightly lower than that in the SIOP trial (18%). Kathleen [17] found that a positive lymph node was greater when more than 7 lymph nodes were sampled in WT. A similar outcome was observed by Ronica [18], who showed that sampling more than 7 lymph nodes is necessary for the adequate staging of WT. Additionally, Amanda [19] used mathematical modeling and revealed that the desired lymph node yield for favorable histology of WT to reduce the risk of false-negative LN sampling to ≤10% is between 6 and 10. Data related to CCSK are lacking; however, CCSK was a progressive tumor compared with WT, and sufficient LNS sampling is an important issue to prevent under-staging and undertreatment. The median number of LNS sampled in our study was only 4, which needs to be improved in further research. CCSK was originally referred to as a "bone-metastasizing renal tumor of childhood" [20] that was identified in the SIOP trial [7]. However, in other series [3,8,9], lung metastasis has an equal or predominant proportion compared with bone metastasis. There were no stage IV CCSK patients in our study. Lung metastasis could be excluded by chest CT scan in the first presentation, and bone metastasis may be missed because a whole body bone scan was not applied in these children. However, during the long-term follow-up period, except for one patient who relapsed with bone metastasis, none of the patients complained of bone discomfort; thus, the possibility of missed bone metastasis was low.

In this study, two children with stage I CCSK accidently received a shorter course of chemotherapy and did not undergo radiotherapy. They both recovered well and free of relapse with follow-up times of 5 years and 9 years. Therefore, is a shorter course of chemotherapy treatment sufficient for stage I patients? John A [21] demonstrated that children with stage I CCSK have excellent survival rates despite the use of varying radiotherapy doses and chemotherapy regimens in the NWTS 1-5 protocols, and the relapse-free and cancer-specific survival rate was 100% at the follow-up examination. Concerning the late complications suffered from radiotherapy and chemotherapy, Filippo [22] proposed the following question: is it time for a less intensive adjuvant treatment for stage I CCSK? However, the opposite view of this opinion was that the 5-year EFS rate was only 71.5% for the 80 children with stage I CCSK in the SIOP trial [7], wherein radiotherapy was implemented in only 2 of these patients, while the 5-year EFS rate was 100% in the NWTS-5 trial [6], wherein all the children received radiotherapy. The children who received radiotherapy in the current study had a superior 5-year EFS of 87.5% and OS of 87.5% compared with patients who did not receive radiotherapy who had a 5-year EFS of 61.3% and OS of 77.8%. Moreover, the preoperative chemotherapy plan was mainly based on imaging without histological proof of the tumor type, which is the same as that in the SIOP trial [7]. A less intensive preoperative chemotherapy regimen only containing VCR and dactinomycin showed no tumor volume reduction in stage I-III CCSK, which was also observed in the current study. Either deficiency of radiotherapy treatment or a weak chemotherapy protocol may bring adverse outcomes to children with CCSK.

Since radiotherapy and intensive chemotherapy have been applied in CCSK, the prognosis has been greatly improved in recent years [5,6,23]. Because CCSK is a rare entity, a number of large series of homogeneously treated CCSK patients has been reported (Table 3) by multicenter alliances in developed regions [6,7,13,24], and only a limited number of series has been reported in developing regions [8,9]. As summarized in Table 3, the 5-year EFS rate and 5-year OS rate reached approximately 80% and 90%, respectively, in developed regions, while worse outcomes were reported in developing regions. In the current study, the 5-year EFS and OS rates were 63.9% and 78.8%, respectively, which are not satisfactory compared with those in developed regions. The deficiency of radiotherapy in most children is a shortcoming compared with the NWTS-5 and JWiTS-2 studies [6,13] and may cause adverse outcomes.

Relapse tumors are the main cause of death. CCSK has the potential to metastasize or relapse after a prolonged disease-free interval, and there was a patient who experienced relapse in the primary site after a 72-month disease-free interval in this study. However, Seibel [6] reported a patient who experienced relapse in the contralateral kidney after 13.6 years, which was the longest time reported in the literature. In addition, Lang [25] also reported a male who experienced relapse in the bladder after 7 disease-free years. The mean relapse time of CCSK in this study is 19 months (range 5–72 months), which is similar to that in reported studies (Table 4).

The relapse pattern of CCSK appears to be different from other reported studies. R. Furtwangler [7] reported that the most common site of relapse was the brain (44.8%) and lungs (44.8%), and the tumor bed relapse rate was only 13.8%. Similarly, Seibel [6] reported that the most common relapse site was the brain (52.17%), and the tumor bed relapse rate was only 4.3%. With intensive chemotherapy, the most common sites of recurrent disease had been changed from the lungs and bones to the brain [5,6]. However, the most common relapse site was the tumor bed in the current study; 9/11 (81.8%) patients relapsed

Table 4
Reported series of clear cell sarcoma of the kidney.

Author and year	Study design	n	EFS	OS	Relapse	Relapse time (years)	Follow-up time (years)
R. Furtwangler 2013	SIOP protocol	191	78% (5-year)	86% (5-year)	29 (15%)	2.0 (0.6–4.1)	6.2 (2.9–7.8)
Seibel 2018	NWTS-5 protocol	108	79% (5-year)	90% (5-year)	23 (21.3%)	2.0 (0.4–13.6)	9.7 (0.7–19.1)
Zekri 2014	Single-center analysis	25	87.8% (3-year)	88.5% (3-year)	1 (4%)	0.83	1 (0.5–3.75)
Hadler 2010	Single-center analysis	14	NA	57%	6 (42.8%)	<1	NA (0.75–7)
Koshinaga 2018	JWiTS-2 protocol	31	82.4% (5-year)	90% (5-year)	5 (16.1%)	NA	4.2 (0.17–9.25)
Current study 2019	Single-center analysis	41	63.9% (5-year)	78.8% (5-year)	11 (26.8%)	1.6 (0.42–6)	3.33 (0.67–10)

in the tumor bed, and brain relapse occurred in only 2 (18.1%) patients. The main difference in the treatment protocol compared with that of NWTS-5 is the implementation of radiotherapy. Of the patients who relapsed at the primary site, only 1 stage III (lymph node metastasis) patient received radiotherapy, and the other 8 patients did not receive radiotherapy. However, in the SIOP study, the most common relapse site of the patients who did not receive radiotherapy was the primary site; only 2/17 (11.76%) patients experienced local relapse, while the others experienced distant region relapse. Whether radiotherapy in CCSK could decrease the risk of relapse in the primary site remains controversial, and more research is needed to discuss the relapse site distribution and the prevention of relapse.

In the SIOP [7] study, Cox regression analysis showed that age younger than 12 months was an independent, significant adverse prognostic risk factor for EFS. A similar outcome was reported in NWTS-5 [6], which reported that children less than 12 months of age at diagnosis had a poorer five-year EFS of 49% and OS of 61% compared with patients older than 12 months of age who had a 5-year EFS of 84% and OS of 89%. The inferior outcome observed was ascribed to a 50% reduction in chemotherapy doses for children <12 months of age. A similar outcome was observed in this study, Cox regression analysis also showed that age younger than 12 months was the only adverse prognostic risk factor for EFS ($p = 0.018$). The 5-year EFS and OS of the rest of the children ($n = 8$) aged less than 12 months were 40% and 38.9%, respectively, indicating a poorer outcome in children who mostly received a 50% reduction in chemotherapy doses. Is a 50% reduction in chemotherapy doses for these children indispensable? More clinical data is needed to clarify this issue.

4. Conclusion

An increase in survival rate has been seen in patients with CCSK, but there is much work to do, especially in developing countries. Improvements are needed for children who receive a 50% reduction in chemotherapy doses and for those who experience relapse. Regarding the relapse pattern, we could not clarify the different relapse patterns in this study. In addition, especially in undeveloped regions, we should pay attention to the importance of radiotherapy and try to improve the outcome of CCSK.

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